Title

Patients Prescribed Anakinra for Acute Gout Have Baseline Increased Burden of Hyperuricemia, Tophi, and Comorbidities, and Ultimate All-Cause Mortality.

Authors

Sharma, Ena
Pedersen, Brian
Terkeltaub, Robert

Publication Date

2019

DOI

10.1177/1179544119890853

Peer reviewed

Patients Prescribed Anakinra for Acute Gout Have Baseline Increased Burden of Hyperuricemia, Tophi, and Comorbidities, and Ultimate All-Cause Mortality

Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders
Volume 12: 1–5

DOI: 10.1177/1179544119890853
SAGE

Ena Sharma[1,2], Brian Pedersen[1,2] and Robert Terkeltaub[1,2]

[1]Department of Medicine, San Diego Veterans Affairs Healthcare System, San Diego, CA, USA.
[2]Division of Rheumatology, Allergy & Immunology, Department of Medicine, University of California, San Diego, La Jolla, CA, USA.

ABSTRACT

OBJECTIVE: The interleukin-1 (IL-1) receptor antagonist anakinra is an effective, off-label option in acute gout flares, when conventional therapy options are narrowed. We performed a retrospective, randomized, case-controlled study to gain clinical insight on baseline factors for gout patients most likely to receive anakinra, and ultimate mortality of those who received anakinra.

METHODS: Of 1451 gout patients seen between January 2003 and January 2015 in a Veterans Affairs (VA) rheumatology group practice, under stringent managed care principles, 13 (100% male), who received anakinra at least once for flares, were compared with 1:4 age- and sex-matched gout controls. Each patient's first rheumatology encounter was studied by factor analysis for variables associated with later anakinra.

RESULTS: At baseline, patients that received anakinra had higher urate burden (palpable tophi [10/13] vs controls [16/52], $P = .003$), serum urate ([10.6 mg/dL] vs controls [7.6 mg/dL], $P < .0001$), and East Asian descent ([7/13] vs [16/52], $P = .041$). The anakinra group had higher ultimate all-cause mortality ([6/13] vs controls [7/52], relative risk [RR] = 3.43, 95% confidence interval [CI] = 1.39-8.48, $P = .0076$). Factor analysis showed baseline visit palpable tophus and statin use to be most strongly associated with later anakinra use. Increased mortality of anakinra users, as per a factorial analysis, was linked more strongly to comorbidities than to anakinra.

CONCLUSIONS: At baseline rheumatology gout encounter, higher urate, palpable tophi, statin prescription, and East Asian descent were associated with later anakinra use for flares. Mortality was more closely associated to the presence of comorbidities at baseline rheumatology visit than to anakinra prescription.

KEYWORDS: Gout, hyperuricemia, arthritis, cytokines, mortality

RECEIVED: October 30, 2019. **ACCEPTED:** November 1, 2019.

TYPE: Short Report

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was made possible through support by the VA Research Service and National Institutes of Health (NIH) (Nos AR060772 and AR075990).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr R.T. has served as a paid consultant to SOBI, but SOBI did not provide support or input to the work conducted in this study. The VA funding source provided salary support for E.S. and R.T. as well as office space, bioinformatics support, and the patient population for analysis in this study. The NIH funding source provided salary support for R.T. and computer resources for this project.

CORRESPONDING AUTHOR: Robert Terkeltaub, Department of Medicine, San Diego Veterans Affairs Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA. Email: rterkeltaub@ucsd.edu

Introduction

Gout is strongly associated with comorbidities, including obesity, metabolic syndrome, type II diabetes, hyperlipidemia, hypertension, chronic kidney disease (CKD), and coronary artery disease.[1-3] Comorbidities frequently restrict conventional treatment options (ie, nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, corticosteroids) for gout flares.[3] Acute gout flares are mediated by NLRP3 inflammasome activation with consequent interleukin-1β (IL-1β) release.[4] Interleukin-1 (IL-1) antagonism, using the IL-1β-specific antibody canakinumab, is approved in Europe for gout flare. Off-label prescription of the soluble IL-1 receptor antagonist anakinra has been reported effective in case series,[5-10] including in hospitalized inpatients.[11-14] Anakinra was noninferior to conventional approved therapies for acute gouty arthritis in a recent controlled trial.[15] To add insight, for clinical medicine, on baseline characteristics, and long-term mortality risk, in patients who ultimately received ⩾1 rheumatologist-prescribed anakinra courses for acute gout, we conducted a randomized, case-control study.

Methods

We focused on a Veterans Affairs (VA) hospital group rheumatology practice, where anakinra pre-authorization was needed, with prescriptions limited to stringent managed care principles, for contraindication or failure of conventional acute gout therapies. VA San Diego Healthcare System Human Subjects Committee ethics board approved (#130245) the study of electronic records of 1451 patients fulfilling 2015 ACR/EULAR gout criteria,[16] and seen by rheumatology between January 1, 2003 and January 27, 2015. All reviewed material was fully de-identified, retrospective information. A total of 13 patients received anakinra for gout flare, with demographics shown in Figure 1.

In retrospective case-control analyses, 4 age- and sex-matched controls were chosen (by randomization) for each patient who received anakinra (Figure 1). Control selection used search criteria in health records: gout diagnosis by International Classification of Diseases—Ninth Revision (ICD-9) coding, ⩾1 visit to VA rheumatology clinic or inpatient rheumatology consultation, and

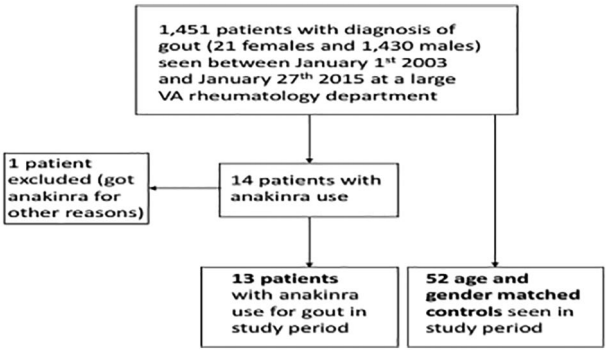

Figure 1. Flow diagram for patient selection and study design. VA indicates Veterans Affairs.

no recorded anakinra use. The first recorded rheumatology clinical encounter during the study period was analyzed. Gout flares were defined by validated criteria.[17] Factor analysis of mixed data (FAMD), to explore similarities between all variables (quantitative and qualitative) for all individuals, was performed using FactoMineR (version 1.39) within the R environment (version 3.4.3).[18,19] Relative risk (RR) was calculated as described by Altman.[20]

Results

At initial rheumatology visit, patients ultimately receiving anakinra more frequently had palpable tophi and higher serum urate (Table 1). There were no significant differences in the mean

Table 1. Overview of demographics of patient populations and clinical profiles.

ALL PATIENTS (N = 65)	ANAKINRA GROUP (N = 13)	CONTROL GROUP (AGE AND SEX MATCHED) (N = 52)	*P* VALUE[a]	*P* VALUE[b]
Clinical profile				
Palpable tophus detected, n (%)	**10/13 (77)**	**16/52 (31)**	**.003**	**.03**
Serum uric acid (mg/dL)	**10.66**	**7.65**	**<.001**	**.02**
Mean number of comorbidities	3.92	3.18	.112 CI = −0.18 to 1.67	.31
Diabetes, n (%)	7 (54)	19 (37)	.35	.58
Hypertension, n (%)	12 (93)	39 (75)	.27	.49
CKD—stage 3 or greater, n (%)	**8 (62)**	**13 (25)**	**.02**	.09
CHF, n (%)	4 (31)	10 (20)	.45	.71
Obesity, n (%)	8 (62)	33 (64)	1.00	1.00
Ethnicity, n (%)				
Black	1 (7)	8 (15)	.67	.87
East Asian	**7 (54)**	**16 (31)**	**.04**	.15
White	5 (39)	29 (56)	1.00	1.00
Hispanic	0 (0)	4 (7)	.58	.84
Medications at baseline, n (%)				
Urate-lowering therapy	7 (54)	17 (33)	.21	.45
NSAIDs	6 (47)	26 (50)	1.00	1.00
Steroids	3 (23)	10 (20)	.72	.87
Colchicine	8 (62)	17 (33)	.11	.31
Metformin	2 (16)	6 (12)	.66	.87
Insulin	3 (23)	5 (10)	.20	.45
Loop diuretics	4 (31)	8 (16)	.24	.47
Statins	**9 (70)**	**15 (29)**	**.01**	.08
Thiazides	1 (8)	3 (6)	1.00	1.00

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs.
Bold font for individual *P* values indicates statistical significance.
[a]Uncorrected *P* values calculated using unpaired *t* tests.
[b]*P* values corrected by the Benjamini-Hochberg procedure for multiple comparisons.

Table 2. Details related to anakinra use and ultimate mortality in the anakinra treatment group.

PATIENT	NUMBER OF COURSES OF ANAKINRA	RESPONSE TO ANAKINRA (DETERMINED BY TREATING PHYSICIAN)	SIDE EFFECTS	RE-FLARE IN 21 DAYS OR LESS	CAUSE OF DEATH, IF APPLICABLE
1	3 courses (100 mg/day × 5 days)	Excellent (complete and rapid response)	None	1 repeat flare in 3 days after the first course. 1 repeat flare at 14 days after the second course	N/A
2	1 course (100 mg/d × 3 days)	Substantial	None	Repeat flare at 7 days post cessation	N/A
3	8 courses (100 mg/d × 3-5 days)	Excellent	Nonspecific malaise, dizziness	Minor flares at different sites within 14 days post cessation for the last 3 flares requiring anakinra	*Clostridium difficile* infection, health-care-associated pneumonia, renal failure
4	1 course (100 mg/d × 3 days)	Excellent	None	Re-flare in 14 days post cessation	N/A
5	1 course (100 mg/d × 3 days)	Lost to follow-up	Lost to follow-up	Lost to follow-up	N/A
6	1 course (100 mg/d × 21 days)	Excellent	Injection site reaction	Re-flare in 14 days post cessation	N/A
7	1 course (100 mg/d × 5 days)	Substantial	None	Flare still ongoing (but improved) at 21 days post anakinra	N/A
8	1 course (100 mg/d × 3 days)	Excellent	None	Lost to follow-up	N/A
9	1 course (100 mg/d × 3 days)	Substantial	None	Re-flare at different sites in <21 days post anakinra	Unknown
10	1 course (100 mg/d × 5 days)	Poor	None	No repeat flare within 21 days	CHF decompensation
11	2 courses (100 mg/d × 3 days)	Substantial	None	No repeat flare within 21 days	Unknown
12	1 course (100 mg/d × 14 days)	Substantial	Injection site reaction	No repeat flare within 21 days	CHF decompensation
13	1 course (100 mg/d × 5 days)	Excellent	None	No repeat flare within 21 days	Unknown

Abbreviations: CHF, congestive heart failure; N/A, not applicable.

number of selected comorbidities (mean of 3.9 in anakinra, 3.1 in controls, $P = .11$, confidence interval [CI] = −0.18 to 1.67; Table 1), but ultimate all-cause mortality was greater in those who had received anakinra for acute flare ([6/13] vs controls [7/52], RR = 3.43, 95% CI = 1.39-8.48, $P = .0076$). East Asian patients were more likely to be treated with anakinra (Table 1).

Most patients had several anakinra courses for gout flares and responded and tolerated anakinra well (not shown). Although the cause of death for several patients in the anakinra treatment group remains unknown, congestive heart failure (CHF) decompensation as precipitant was confirmed in 2 and septic shock (approximately 12 months from the last anakinra dose) in 1 who had received the most courses of anakinra (Table 2). By comparison, of 52 controls, 7 died during the study period (Table 2). Two patients were found dead at home and 3 died from complications of metastatic neoplasms. One with end-stage renal disease had a cardiac arrest during dialysis and 1 with neurogenic bladder died from renal failure, after declining dialysis.

Factor analysis of mixed data was applied to the qualitative variables shown in Figure 2, as well as estimated glomerular filtration rate (eGFR), total number of comorbidities per individual, and uric acid level (quantitative variables), for all individuals. Here, 35.51% of total variance of the data is represented within the first 2 dimensions. Eventual anakinra use was most strongly associated with baseline palpable tophus, and statin or urate-lowering therapy (ULT), which was exclusively allopurinol. There was distinct clustering, with either insulin or loop

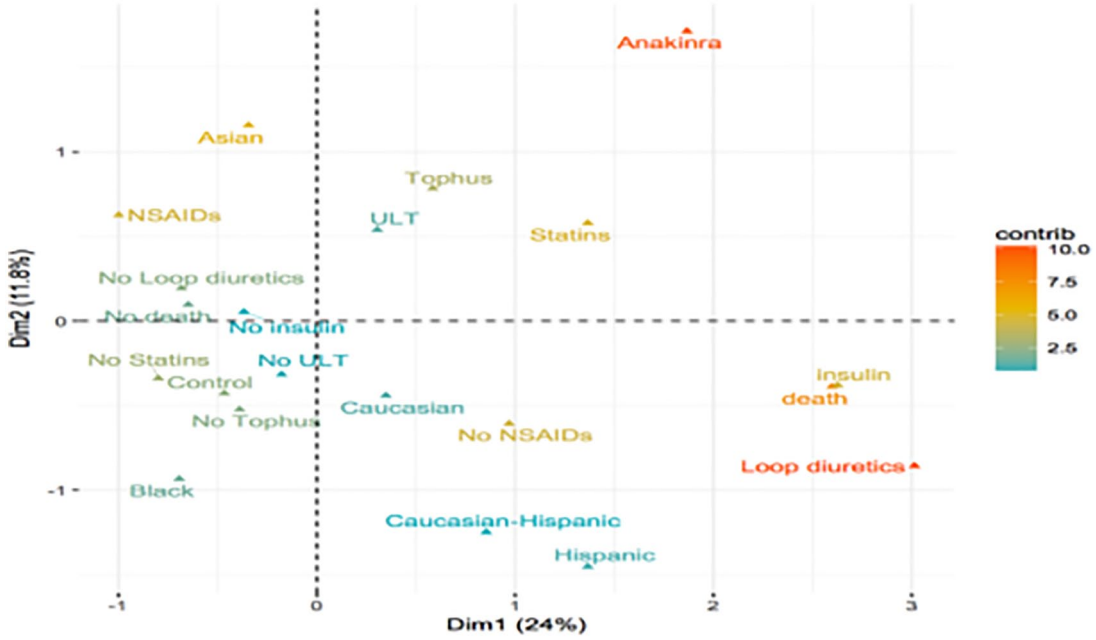

Figure 2. Contribution of categorical variables to the first and second dimensions of a factor analysis of mixed data. Categories of the categorical data groups are labeled on the plot regarding their contribution to the first dimension (*x*-axis) and the second distinct grouping of death with either insulin or loop diuretic use. Dim 1 indicates dimension 1 representing 24% of the variance of the analyzed variables; NSAIDs, nonsteroidal anti-inflammatory drugs; ULT, urate-lowering therapy; Dim2, dimension 2 representing 11.8% of the variance of the analyzed variables.

diuretic use, of death during the observation period (Figure 2). Increased mortality with antecedent anakinra prescription for acute gout essentially was linked strongly to comorbidities (Figure 2).

Discussion

Our study highlights that one of the strongest predictors of anakinra use for gout flare treatment is that other options are constrained by comorbidities. Patients requiring anakinra also were more likely to have greater serum urate elevation and tophaceous disease at baseline visit, East Asian descent, and, at the end of the observation period, higher mortality. Bevis et al[21] identified 4 clusters in a cross section of gout comorbidity clustering: C1 (elderly with frequent gout attacks; 97% with CKD), C2 (isolated gout and frequent alcohol intake), C3 (hypertension, diabetes, hyperlipidemia, coronary heart disease, and/or CKD were most prevalent and this group had the highest frequency prescription of ULT), and C4 (obese and with hypertension). Here, anakinra recipients appeared to fall under cluster 3, with associated ULT and statin use. Gout is associated with premature mortality.[22] Here, the death signal on factor analysis was tightly linked to insulin and loop diuretic use, thereby implicating comorbid diseases. Patients with more comorbidities, especially atherosclerosis, could have elevated systemic inflammation, potentially predisposing to more severe attacks of gout. Cardiovascular disease is more prevalent in gout than controls.[23] Here, 22% of all patients had CHF and 81% had hypertension. East Asians (particularly Pacific Islanders) were disproportionately represented in anakinra recipients, but confounders and bias as well as low subject numbers may have contributed to this observation. Larger-scale studies would be indicated to identify and validate any potential genetic predisposition, such as by *ABCG2* variant Q141K,[23] to higher inflammatory state and comorbidities in gout.[24]

Limitations of this study include that case-control studies have high susceptibility to bias, but performing the study in the same VA group was an effort to reduce such issues. A relatively complex VA patient population with prevalent comorbidities was examined, which, as in other VA-based studies, imposes contraindications to the use of NSAIDs, colchicine, or corticosteroids.[3] Additional limitations included exclusively retrospective analyses, small sample size, men only receiving anakinra, and quite high prevalence of minority ethnic and racial groups.

In summary, the patient profile for anakinra prescription for acute gout was associated with specific characteristics at baseline rheumatology visit. These included uncontrolled hyperuricemia and a high body urate burden (reflected by palpable tophi), as well as East Asian descent, and a significantly increased number of comorbidities that could heighten systemic inflammation and predispose to continuing symptomatic gout. The increased all-cause mortality signal in this study, associated with prior use of anakinra for acute gout flare, was linked to higher comorbidity burden, especially cardiovascular disease.

Author Contributions

Each of the authors contributed to: Obtaining data, Interpreting data, writing and editing the manuscript.

Data Sharing

All final peer-reviewed manuscripts that arise from these data will be submitted to the digital archive PubMed Central. Wherever applicable, data will be deposited to appropriate public repositories (eg, dbGAP) or made available to investigators who request such information. De-identified data may be shared in the form of Excel spreadsheets, or in database or SAS dataset format. Documentation (data dictionary, etc) will be included to allow others to use the data.

ORCID iD

Robert Terkeltaub https://orcid.org/0000-0001-5368-7473

REFERENCES

1. Dalbeth N, Merriman TR, Stamp LK. Gout. *Lancet*. 2016;388:2039-2052.
2. Igel TF, Krasnokutsky S, Pillinger MH. Recent advances in understanding and managing gout. *F1000Res*. 2017;6:247.
3. Keenan RT, O'Brien WR, Lee KH, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. *Am J Med*. 2011;124:155-163.
4. So A, Dumusc A, Nasi S. The role of IL-1 in gout: from bench to bedside. *Rheumatology (Oxford)*. 2018;57:i12-i19.
5. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther*. 2007;9:R28.
6. Ottaviani S, Molto A, Ea HK, et al. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. *Arthritis Res Ther*. 2013;15:R123.
7. Chen K, Fields T, Mancuso CA, Bass AR, Vasanth L. Anakinra's efficacy is variable in refractory gout: report of ten cases. *Semin Arthritis Rheum*. 2010;40:210-214.
8. Rossi-Semerano L, Fautrel B, Wendling D, et al. Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. *Orphanet J Rare Dis*. 2015;10:Article19.
9. Loustau C, Rosine N, Forien M, et al. Effectiveness and safety of anakinra in gout patients with stage 4–5 chronic kidney disease or kidney transplantation: a multicentre, retrospective study. *Joint Bone Spine*. 2018;85:755-760.
10. Desmarais J, Chu CQ. Utility of anakinra in acute crystalline diseases: a retrospective study comparing a university hospital with a Veterans Affairs medical center. *J Rheumatol*. 2018;46:748-750.
11. Aouba A, Deshayes S, Frenzel L, et al. Efficacy of anakinra for various types of crystal-induced arthritis in complex hospitalized patients: a case series and review of the literature. *Mediators Inflamm*. 2015;2015:792173.
12. Thueringer JT, Doll NK, Gertner E. Anakinra for the treatment of acute severe gout in critically ill patients. *Semin Arthritis Rheum*. 2015;45:81-85.
13. Ghosh P, Cho M, Rawat G, Simkin PA, Gardner GC. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. *Arthritis Care Res (Hoboken)*. 2013;65:1381-1384.
14. Liew JW, Gardner GC. Use of anakinra in hospitalized patients with crystal-associated arthritis. *J Rheumatol*. 2019;46:1345-1349.
15. Janssen CA, Oude Voshaar MAH, Vonkeman HE, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. *Rheumatology (Oxford)*. 2019. doi:10.1093/rheumatology/key402.
16. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2015;74:1789-1798.
17. Gaffo AL, Schumacher HR, Saag KG, et al. Developing a provisional definition of flare in patients with established gout. *Arthritis Rheum*. 2012;64:1508-1517.
18. Lê S, Josse J, Husson F. FactoMineR: an R package for multivariate analysis. *J Stat Softw*. 2008;25:253-258.
19. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: The R Foundation for Statistical Computing. http://www.R-project.org/
20. Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall; 1991.
21. Bevis M, Blagojevic-Bucknall M, Mallen C, Hider S, Roddy E. Comorbidity clusters in people with gout: an observational cohort study with linked medical record review. *Rheumatology (Oxford)*. 2018;57:1358-1363.
22. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation*. 2007;116:894-900.
23. White WB, Chohan S, Dabholkar A, Hunt B, Jackson R. Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities. *Am Heart J*. 2012;164:14-20.
24. Cleophas MC, Joosten LA, Stamp LK, Dalbeth N, Woodward OM, Merriman TR. ABCG2 polymorphisms in gout: insights into disease susceptibility and treatment approaches. *Pharmgenomics Pers Med*. 2017;10:129-142.